

**Appl. No.** : **09/315,292**  
**Filed** : **May 20, 1999**

### **REMARKS**

Applicants have canceled all pending claims without prejudice to, or disclaimer of, the subject matter contained therein. Applicants maintain that the cancellation of a claim makes no admission as to its patentability and reserve the right to pursue the subject matter of the cancelled claim in this or any other patent application.

Applicants have added new claims 99-119. Support for these claims can be found throughout the specification as filed, for example, at original claims 37-51; page 16, lines 25-28; page 23, lines 7-10 and 30-34; page 34, lines 9-31; and Examples 2 and 3, beginning on page 61.

#### 35 U.S.C. § 112, First Paragraph – New Matter

Claims 66, 70-75 and 78-98 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement because they contain impermissible new matter. Applicants respectfully traverse.

Applicants submit that the previously filed amendments were adequately described in the specification as filed, and therefore do not constitute new matter. The Examiner's argument that the "specific oligonucleotides are not sufficient to demonstrate support for the entire genus of molecules recited in the claims," *Office Action* at 4, is without support in the caselaw or written description guidelines. However, Applicants have canceled claims 66, 70-75 and 78-98, without prejudice to, or disclaimer of, the subject matter contained therein, rendering this rejection moot.

#### 35 U.S.C. § 103(a) – Obviousness

Claims 66, 70-75 and 78-98 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Nyce *et al.*, in view of Nicklin *et al.* and Yu *et al.*, for the reasons of record. *Office Action* at 5. In response, Applicants argued that the cited references did not teach each and every limitation of the pending claims, and that the Examiner had not provided a reason for one of skill in the art to choose the a particular combination of modifications from the three cited references to arrive at the claimed method. The Examiner has rejected these arguments, stating that the selection of the recited modifications and sizes in the claimed method "is considered within the realm of routine optimization." *Office Action* at 10. Applicants respectfully traverse.

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Applicants have canceled claims 66, 70-75 and 78-98, without prejudice to, or disclaimer of, the subject matter contained therein. Pending claim 99 recites:

99. A method for administering an oligonucleotide into a lung of a mammal, said method comprises:  
aerosolizing an oligonucleotide ; and  
introducing the aerosolized oligonucleotide into the lung of a mammal,  
wherein the aerosol particles have a size of about 1 to about 5 microns, wherein said oligonucleotide is about 8 to about 30 nucleotides in length, wherein a plurality of said nucleosides in said oligonucleotide are 2'-O-methoxyethyl nucleosides, wherein at least one internucleotide linkage within said oligonucleotide is a phosphorothioate linkage, and wherein said oligonucleotide is taken up by at least one cell type in the lung of the mammal.

Applicants submit that the cited references, alone or in combination, do not disclose or suggest the method claimed in pending claim 99. Nor is it obvious to modify the method disclosed in Nyce *et al.* to arrive at the instantly claimed method. The Examiner has previously stated that one of skill in the art could arrive at Applicants' claimed method through "routine optimization."

As held in *In re Waymouth and Koury*, 182 USPQ 290 (CCPA 1974), when it is necessary to modify the teachings in the art in order to arrive at the claimed subject matter, obvious experimentation must be evaluated according to the teachings of the prior art, including teachings away from the claimed subject matter:

In determining whether or not such [obvious] experimentation is within the teachings of the art, we "must be ever alert not to read obviousness into an invention of the basis of the [appellants'] own statements; that is we must view the prior art without reading into that art [appellants'] teachings."

In so viewing the reference, we find that the only experimentation for achieving better [results according to prior art teachings] ... would definitely lead one of ordinary skill in the art away from appellants' claimed ratio. *In re Waymouth and Koury*, 182 USPQ 290, 292-293 (CCPA 1974) (internal citations omitted).

In the instant case, Nyce *et al.* does not disclose a method using an oligonucleotide wherein the "a plurality of said nucleosides in said oligonucleotide are 2'-O-methoxyethyl nucleosides," as recited in claim 99. While Yu *et al.* does disclose the use of 2'-modified oligonucleotides, Tables 1 and Table 2 teach away from modifying Nyce *et al.* to incorporate a plurality of said 2'-O-methoxyethyl nucleosides in the oligonucleotide.

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Molecules 1-6 of Yu *et al.* were tested for their ability to inhibit HIV-1, with molecules 2-4 differing in the number of 2'-modified phosphodiester nucleosides included. Table 2 demonstrates that molecule 4, which had the most 2'-modified nucleosides, had the worst activity, while molecule 2, which had the fewest 2'-modified nucleosides, had the best activity of molecules 2-4. While molecules 2-4 also had different amounts of phosphodiester internucleoside linkages, molecules 1 and 6 differ only in the number of 2'-modified nucleosides. Importantly, the molecule with the best activity reported in Table 2 contains zero 2'-modified nucleosides, although it is only slightly better than the molecule 6, which contains several 2'-modified nucleosides. Thus, when taken together, Table 2 of Yu *et al.* would not lead one of skill in the art to modify the molecule of Nyce *et al.* to include a plurality of 2'-modified nucleosides, since Table 2 suggests that the more 2'-modified nucleosides that are included, the worse the molecule performs, and having no 2'-modified nucleosides is best.

In addition, as Applicants have previously noted, one must also modify Yu *et al.* to replace the 2'-O-methyl nucleosides with 2'-O-methoxyethyl nucleosides as claimed. While Nicklin *et al.* does disclose a 2'-O-methoxyethyl modification, it is one of more than 90 different 2'-modifications. One of skill in the art would have no basis to believe that replacing 2'-O-methyl nucleosides with 2'-O-methoxyethyl nucleosides would change the outcome of Yu *et al.*'s results shown in Table 2. Therefore, even when all three references are combined, the Examiner has failed to establish that the claimed method is *prima facie* obvious, since the cited art teaches away from the claimed method.

Finally, even if the Examiner has established a *prima facie* case of obviousness, a point which Applicants do not concede, Applicants submit that the claimed method provides unexpected results. Applicants note that §2141 ¶ III of the M.P.E.P., titled “**Objective Evidence Must Be Considered**,” states that: “Objective evidence or secondary considerations such as unexpected results...are relevant to the issue of obviousness and must be considered in every case in which they are present. When evidence of any of these secondary considerations is submitted, the examiner must evaluate the evidence.” M.P.E.P. §2141 ¶ III (emphasis added).

Contrary to the teachings of Yu *et al.*, Applicants have found that incorporating more 2'-modified nucleotides unexpectedly improves the uptake of oligonucleotides, which will result in improved activity for the same amount of oligonucleotide. Example 3 of the instant application

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discloses the results of *in vivo* administration of aerosolized nucleotides into the lung. Tables 2 and 3 shows the concentration of oligonucleotide in the lungs of mice following single and multiple administrations, respectively, of three antisense molecules. Importantly, ISIS 15163 performs as much as 4 times better than ISIS 17009, even though the only difference between the two molecules is the fact that ISIS 17009 does not contain any 2'-modified nucleosides, while ISIS 15163 does. Because uptake of the molecule is directly related to its activity, this is clearly unexpected in view of Yu *et al.*, which shows that the inclusion of 2'-modified nucleosides at best has no effect, and at worst decreases the activity of the molecule.

In view of the above, Applicants submit that the pending claims are patentable over Nyce *et al.*, in view of Nicklin *et al.* and Yu *et al.*

#### Claim Objections

Claim 92 is objected to because it does not end with a period. Applicants have canceled this claim, without prejudice to, or disclaimer of, the subject matter contained therein, rendering the objection moot.

#### 35 U.S.C. § 112, Second Paragraph – Indefiniteness

Claims 66, 70-75, and 78-98 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for insufficient antecedent basis for "said first and second wing segments." Applicants have canceled these claims, without prejudice to, or disclaimer of, the subject matter contained therein, rendering the rejection moot.

#### No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, the Applicants are not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. The Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior

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prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that the Applicants have made any disclaimers or disavowals of any subject matter supported by the present application.

**Patents and Applications**

Applicant wishes to draw the Examiner's attention to the following patents or applications of the present application's assignee. Applicants encourage the Examiner to review and monitor the prosecution of the following patents and/or applications throughout the pendency of this application.

<b>Patent / Serial Number</b>	<b>Title</b>	<b>Issued / Filed</b>
09/083,586	COMPOSITIONS AND METHODS FOR THE PULMONARY DELIVERY OF NUCLEIC ACIDS	5/21/1998

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### CONCLUSION

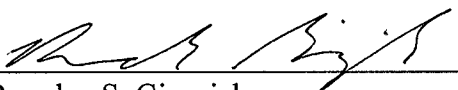
In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 2/15/08

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